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Human fetal oxygenation ($tcPo_2$), heart rate variability and uterine activity following maternal administration of meperidine

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1 Introduction

Continuous fetal heart rate (FHR) monitoring coupled with intermittent microsampling of fetal capillary blood for acid-base status is one of the objective methods for the evaluation of the effects of a pharmacologic agent on the fetus. Prior to the availability of these techniques, neonatal outcome was the only parameter available to test the effect of a pharmacologic agent on the fetus in clinical practice. FHR variability as seen in a FHR tracing is a clinical indicator of the fetal neurocardiovascular integration [11]. Various drugs have been demonstrated to alter FHR variability [4, 12, 13, 16].

A close approximation of human fetal oxygenation can be measured continuously with the use of a transcutaneous osygen electrode during the active phase of labor [8]. Although HUCH et al. [7] have reported a decline in human maternal $tcPo_2$ following the administration of 50 or 100 mg meperidine intramuscularly, fetal $tcPo_2$ was not measured. LÖFGREN reported that FHR variability lags behind transcutaneous Po_2 ($tcPo_2$) changes by some time [10]. The purpose of this study is to evaluate the relationship of fetal oxygenation to FHR variability and uterine activity following the maternal administration of 50 mg intravenous meperidine and to describe the temporal relationship of alterations in FHR variability to changes in fetal $tcPo_2$ and uterine activity in the human.

2 Patients and procedures

Ten patients from the Sloane Hospital for Women at the Columbia-Presbyterian Medical Center in New York underwent $tcPo_2$ evaluation of fetal oxygenation, fetal heart rate variability and uterine activity. All patients in this study were in the active phase of uncomplicated labor, maintaining one position with cervical dilatation between three and eight centimeters at the onset of the study. The demographic characteristics of these patients are given in table I. No patient received any medi-

Table I. Demographic characteristics of patients receiving intravenous administration of 50 mg of meperidine.

Place and nature of study	No. of patients	Age Range	Parity	Maternal weight (lbs)	Neonatal weight (gms)	Apgar score (5 min)
Sloane Hospital Fetal oxygenation ($tcPo_2$) UA (Montevideo units)	10	24.7 (18–32)	0.4 (0–2)	150 (122–176)	3088 (2750–3660)	8.8 (8–9)
Women's Hospital FHR variability (DI, II) and uterine activity (UAU)	20	23.8 (14–43)	2 (0–10)	150 (116–175)	3395 (2760–4330)	9 (7–10)

cation, with the exception of oxytocin which when used was infused at a constant rate throughout the evaluation period. The dosage and timing of meperidine administration was determined by the managing obstetrician using standard clinical indicators. Patients were monitored using an FHR electrode and an intrauterine catheter. Uterine activity was measured by an open ended transcervical intrauterine catheter connected by a strain gauge placed at the level of the patient's sternum and quantitated either with Montevideo units or by measuring the area under the uterine pressure curve (uterine activity units) with an on-line technique utilizing a voltage control oscillator [6].

Fetal oxygenation was measured continuously by a transcutaneous Po_2 ($tcPo_2$) electrode in ten patients in the manner described by HUCH [8]. The $tcPo_2$ measurements are based on the polarographic technique by which the skin is warmed to 43 °C and a deflection in the current between platinum cathode and silver anode, caused by molecular oxygen diffusing from the fetal epidermis, is recorded as $tcPo_2$ (Oxymonitor, Litton Co., Chicago). These electrodes are in an electrolyte solution and covered by a teflon membrane which is permeable to oxygen and in contact with the tissue from which $tcPo_2$ is to be measured [3, 5]. The validity of this technique in this laboratory has been established by comparing $tcPo_2$ values with fetal scalp capillary Po_2 and umbilical arterial and venous Po_2 values [1].

Following shaving of the fetal scalp, the $tcPo_2$ electrode was applied to the presenting part with an histoacrylic glue. The $tcPo_2$ electrode was appropriately calibrated prior to use, and at the termination of the observation period, $tcPo_2$ was correlated with either the capillary Po_2 value or with Po_2 from umbilical arterial or venous blood whenever possible. After stabilization of $tcPo_2$ readings, a control or preinjection measurement and recording were obtained. Meperidine was then administered intravenously over a two-minute interval.

From the ten patients in New York, the interval from the injection to the onset of decline and the maximum decline in $tcPo_2$ levels were recorded. The duration of the maximum decline in $tcPo_2$ and the interval for a return to a recovery baseline were also observed. Visually evaluated changes in FHR variability and uterine activity (Montevideo units) were marked and temporal means were obtained. Due to technical problems, computer derived indices of FHR variability and uterine activity could not be accomplished in New York.

At the same time, one of the investigators was carrying out almost identical studies at the Los Angeles County-University of Southern California Medical Center. Fetal heart rate and uterine activity data from twenty patients identically managed (by the same protocol) and demographically matched at the Los Angeles County-University of Southern California Medical Center were evaluated as follows. The comparison of the two groups of patients is given in table I. FHR variability was computed from the "R-R" intervals obtained from the fetal ECG signals which had been recorded at a speed of $1-7/8$ inches per second onto analog magnetic tape using a high fidelity tape recorder (Ampex PR 500 or Ampex 1260). The beat-to-beat interval indices were calculated according to the method of YEH, FORSYTHE and HON [15] using a PDP-8/1 or PDP-11 computer (Digital Equipment Corporation).

The differential index (DI) or short-term variability (the standard deviation of the sequential "R-R" interval differences) and the interval index (II) or long-term variability (the coefficient of variation of the standard deviation of the "R-R" intervals) in sequential fifteen second windows within each five minute segment were averaged and expressed as the mean DI and II for that five-minute segment of baseline FHR. The five-minute averaging process was repeated every five minutes for a one-half hour pre-injection period and for the duration of the measured post-injection period. Finally the mean value of each index for each of the five-minute time segments was then calculated for the group of twenty patients.

Uterine activity (torr minutes, uterine activity units) was summed for each ten-minute interval of the preinjection and postinjection period. Linear regression analyses of the pre- and postinjection data for uterine activity was utilized to compare the differences of slopes between expected uterine activity and the actual observed uterine activity.

3 Results

Fetal oxygenation measurements ($tcPo_2$) from the ten New York patients who received 50 mg intravenous meperidine are presented in table II. In these patients the mean preinjection baseline $tcPo_2$ was 18.6 torr. A decline in $tcPo_2$ was noted at 3.13 minutes following the injection. The mean

Table II. Effects of 50 mg intravenous meperidine on fetal $tcPo_2$ (by individual patient).

Case no.	Preinjection $tcPo_2$ (torr)	Injection decline interval (min)	Injection maximum decline interval (min)	Duration of maximum decline (min)	Lowest $tcPo_2$ value (torr)	Injection baseline recovery (min)	Percent decline	Fetal scalp capillary pH	Umbilical venous/arterial (UV/UA) pH	Po_2	BE	Associated factors
1	27	2.33	12.0	7.0	14	23.0	48	–	7.35 7.28	– –	– 5.2 – 6.7	Repeated variable deceleration, body cord,
2	18	2.67	4.33	3.0	12	7.33	33	7.30	7.27 7.19	41 23	−11.8 −14.6	Nuchal cord x1, repeated variable decelerations
3	24	2.33	13.0	6.5	5	21	79	7.27	7.22 7.14	25 17	– 8.6 −10.3	Thick meconium
4	8	2.67	11.33	2.33	2	15	75	–	–	–	–	Emesis, patient fast asleep
5	16	3.67	6.0	1.67	7	9.33	56	7.28	7.27 7.22	24.7 16	– 7.3 – 7.7	Nuchal cord
6	18	7.67	9.33	14.0	16	29.0	11	–	7.28 7.17	31.4 21	– 7.8 – 8.8	
7	24	4.0	5.67	4.0	18	19.0	25	–	–	–	–	
8	18	2.33	5.33	2.0	16	8.33	11	7.22	–	–	–	Nuchal cord, caput, oxytocin infusion
9	19	1.67	3.67	4.33	15	8.67	21	7.28	7.3	19.3	– 3.2	
10	14	2.0	4.33	1.33	12	12.33	14		7.32 7.22	32.1 19.1	– 1.6 – 4.5	Variable deceleration, supine hypotension prior to $tcPo_2$ electrode application
mean ± SD	18.6 ± 5.48	3.13 ± 1.75	9.0 ± 3.55	4.61 ± 3.83	11.7 ± 5.31	15.29 ± 7.41	37.4 ± 25.8		7.35 7.27	28.4 14.5	– 3.8 – 4.9	

maximum decline value in $tcPo_2$ (11.7 torr) which lasted for an average of 4.5 minutes, was noted 9 minutes after the injection. This decline was statistically significant (t test, $P < 0.01$). The mean recovery baseline $tcPo_2$ of 15.0 torr was reached after an average of 15.29 minutes, $\pm$ 7.68 from the onset of the injection. There was a direct correlation between injection to onset of decline interval and the duration of maximum decline ($r = 0.75$); as well as between duration of maximum decline and baseline recovery ($r = 0.85$).

The visually evaluated FHR variability data (from New York) was compared to the computer derived data (from the California patients) and were found to correlate almost identically. A similar correlation was found for uterine activity data measured in Montevideo units and uterine activity units.

The mean fifteen second window representing the first five minute segment of baseline long- and short-term variability following the injection of meperidine was noted to rise slightly, and the second five-minute interval began to decrease which continued for each five-minute interval until a maximum depth was reached at 25 minutes with a return toward normal values by 30 minutes postinjection.

The decline in $tcPo_2$ and a transient increase in FHR variablity (followed immediately by decrease in the indices of FHR variability), after the injection of meperidine is associated with a decrease in uterine activity which is different from the normal positive slope curve of unmedicated uterine activity. This shift in uterine activity is significant ($P < 0.05$, paired "t" test). The temporal relationship of fetal $tcPo_2$, baseline long and short term variability (quantitated computer derived indices) and uterine activity following the injection of 50 mg of intravenous meperidine are given in figure 1.

The $tcPo_2$ values, FHR variability indices, and uterine activity changes in one patient receiving 75 mg of intravenous meperidine were similar to those obtained in patients receiving 50 mg meperidine; however, no changes in $tcPo_2$ were noted in two patients who received 25 mg intravenous meperidine.

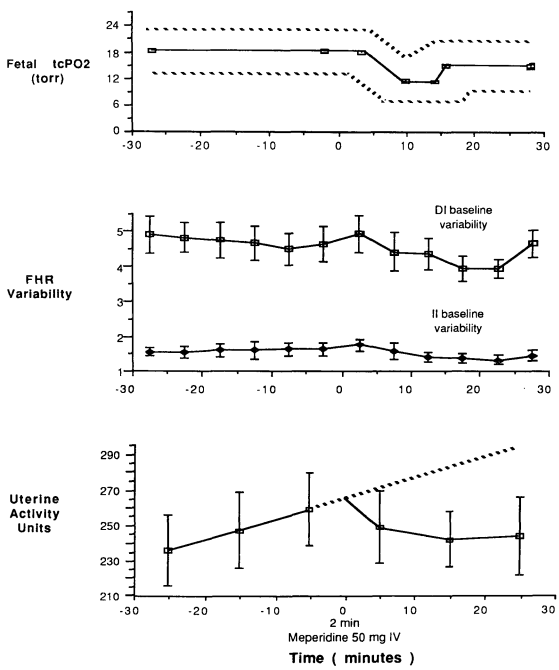

Figure 1. Fetal $tcPo_2$, FHR variability (short term – DI, long term – II) and uterine activity (uterine activity units) $\pm$ S.E. following a two-minute injection of 50 mg meperidine at time 0 minutes.

4 Discussion

These data indicate that there is a decline in fetal $tcPo_2$ values shortly following intravenous injection of 50 mg meperidine. The lowest level of oxygenation is noted approximately seven minutes following the beginning of the injection. The duration of maximum decline lasts for approximately five minutes, and the $tcPo_2$ shortly returns to a recovery baseline at a slightly lower level than the preinjection oxygenation value. Analysis of FHR variability indicates that there is a decrease in short and long term indices of FHR variability which is noted at the 10 minute postinjection interval following a short increase in indices at 5 minutes between five and ten minutes following the injection. This decline lasts for approximately 15 minutes with an initiation of return toward normal baseline levels at 30 minutes postinjection. Uterine activity is noticed to decrease almost immediately following the intravenous injection of 50 mg of meperidine. This suggests that changes in fetal $tcPo_2$ values precede those in FHR variability. Although a decrease in maternal oxygenation following meperidine injection has been reported by HUCH et al. [7], the correlation between FHR variability, fetal $tcPo_2$ changes and uterine activity have not been reported.

The mechanism for the transient fall in fetal oxygenation is not well understood. Inasmuch as abnormal umbilical cord positioning and FHR variable decelerations were noted in a number of patients, some meperidine induced exaggeration in the reflex mediated release of acetyl choline at the fetal sino-atrial node may be considered as a potential mechanism. Constriction of the uterine vasculature or fetal peripheral vasoconstriction due either to the drug or fetal hypotension can also represent possible etiologies. HUCH et al. [7] demonstrated that there is a relationship between the administration of meperidine and a decrease in maternal respiratory effort. Perhaps this may be a possible contributor to a decline in fetal $tcPo_2$, when observed; maternal emesis can be an additonal factor.

The slight increase in indices of FHR variability at five minutes postinjection probably represents an alteration in the Po_2/Pco_2 relationship. This change most probably is mediated by the barochemoreceptors. This pattern of shift in FHR variability with fetal hypoxia was first described by STANGE et al. [14] and later supported by other investigators including MILLER et al. [12].

No additionally significant FHR changes other than in indices of FHR variability were noted in these patients nor were there any shifts of perinatal morbidity secondary to this transient change in oxygenation. In contrast to a longer temporal interval of transient decrease in fetal $tcPo_2$ levels which are seen with paracervical block [2], the transient decrease in $tcPo_2$ following meperidine injection was not felt to have clinical significance; nevertheless, in management of fetuses with borderline oxygenation, this observation should be considered, particularly when other procedures and techniques are utilized in which synergy could lead to clinically overt fetal hypoxic problems. A significant decline in fetal $tcPo_2$ seen in some patients may be due to peripheral vasoconstriction resulting from elevated fetal catecholamines or for technical reasons due to caput and moulding of fetal head and/or compression of electrode in advanced labor [9].

The use of quantitated FHR variability from a second but demographically matched and identically managed group of patients was of major assistance to demonstrate quantitation of FHR data only. The changes in FHR variability data had already been appreciated visually, the quantitated data were used to enhance the demonstration of the $tcPo_2$-FHR variability relationship.

The analysis of uterine activity data by both methods demonstrated a diminution following the intravenous injection of 50 mg of meperidine. This indicates that the transient decrease in fetal oxygenation following meperidine injection is probably not due to decreased intervillous space blood flow secondary to increased uterine activity, although this possibility cannot be totally eliminated since approximately 10 percent of the patients have been observed to have an increase of uterine activity following the injection of this dose of meperidine.

For completeness, intravenous doses of 25 mg and 75 mg of meperidine has been evaluated using this protocol in a few patients. Meperidine 25 mg administered intravenously causes no change in $tcPo_2$ readings and only very minimal changes in FHR variability and uterine activity. Changes very similar to, but somewhat more pronounced, than those described for 50 mg intravenous meperidine wer recorded when meperidine 75 mg was administered intravenously.

Summary

Fetal $tcPo_2$ levels were measured in 10 patients following maternal administration of 50 mg of meperidine by intravenous route. About 3 minutes following injection of meperidine, $tcPo_2$ values started to decline to reach the lowest value of 37 $\pm$ 25% by 7 mins of injection. $tcPo_2$ values recovered by about 15 mins following injection. These changes in fetal $tcPo_2$ levels preceded transient minimal increase in FHR variability. The increase in FHR variability was followed immediately by a decrease in the indices of the FHR variability. The uterine activity began to decline below the predicted positive slope values shortly following injection of meperidine. This decline was maximum 15 mins post-injection, subsequently establishing a trajectory toward the positive values expected for unmedicated labor.

Two patients receiving 25 mg intravenous meperidine demonstrated no decline in $tcPo_2$ levels; however, in the patient receiving 75 mg of intravenous meperidine, the changes noted were similar to those observed following 50 mg of meperidine.

Keywords: Fetal oxygenation, fetal heart rate variability, meperidine, $tcPo_2$, uterine activity.

Zusammenfassung

Fetale Oxygenierung ($tcPo_2$), Herzfrequenzvariabilität und uterine Aktivität nach Gabe von Dolantin® an die Mutter

Dolantin® ist das am häufigsten eingesetzte Analgetikum unter der Geburt. Um die Auswirkungen einer intravenösen Dolantingabe auf die fetale Oxygenierung zu erfassen, wurde bei zehn Patienten mit geringen Risikofaktoren in der aktiven Geburtsphase eine kontinuierliche transkutane Sauerstoffpartialdruckmessung ($tcPo_2$) durchgeführt. Bei der Auswertung zeigte sich, daß es zu einem vorübergehenden Abfall der $tcPo_2$-Spiegel kommt, der kurz nach der intravenösen Dolanthingabe einsetzt. Etwa 15 Minuten nach der Injektion stellt sich ein neuer Spiegel ein, der nur geringfügig niedriger als der vor der Injektion ist. Darüber hinaus weisen die Ergebnisse auf einen möglichen Zusammenhang zwischen dem Abfall des $tcPo_2$-Spiegels und der Herzfrequenzvariabilität (FHR) und uterinen Aktivität hin. Um diesen Zusammenhang genauer zu überprüfen, wurden weitere 20 Patienten überwacht, die nach demografischen Kriterien den ersten 10 Patienten mit $tcPo_2$-Monitoring zugeordnet wurden. Bei diesen zusätzlichen 20 Patienten war, durch Protokolle nachgewiesen, das geburtshilfliche Management identisch, jedoch wurde ein Standard-Monitoring durchgeführt, wobei sowohl die quantitative Herzfrequenzvariabilität mit Lang- und Kurzzeitindizes angegeben wurde wie auch die uterine Aktivität, wobei die Fläche unter der Aktivitätskurve mit einem Oszillator gemessen wurde.

Der mittlere $tcPo_2$-Spiegel vor Injektion lag bei 18.6 torr. Das Zeitintervall von der Dolantingabe bis zum initialen Abfall betrug 3.13 ± 1.75 Minuten und bis zum Maximum des Abfalls 9.0 ± 3.55 Minuten. Die Dauer des Abfalls betrug 4.61 ± 3.83 Minuten, der niedrigste $tcPo_2$-Spiegel 11.7 ± 5.31 torr. Zwischen der Dolantininjektion und dem Einstellen einer neuen Basislinie lag ein Zeitintervall von 15.29 ± 7.41 Minuten und ein mittlerer $tcPo_2$-Abfall von 47.4 ± 25.8%. Nach der Injektion lag der $tcPo_2$-Wert bei 15 torr. Nach der $tcPo_2$-Messung wurde ein pH-Wert aus dem fetalen Scalp bestimmt, der mit den venösen und arteriellen Blutgaswerten in der Nabelschnur bei Geburt verglichen wurde. Im allgemeinen gab es eine gute Übereinstimmung zwischen dem letzten Scalp-pH und den umbilikalen Blutgaswerten. Bei Änderung des fetalen $tcPo_2$-Spiegels kam es zu minimalen kurzfristigen Zunahmen der FHR-Variabilität. Danach fielen die Indizes ab, und mit Restabilisierung der $tcPo_2$-Werte wurden schließlich die Werte der neuen, nur geringfügig niederigeren Basislinie nach Injektion wieder erreicht. Dolantin® induziert Veränderungen des $tcPo_2$ und der FHR-Variabilität, welche eng miteinander gekoppelt sind.

Kurz nach der intravenösen Gabe von 50 mg Dolantin® sinkt die uterine Aktivität unterhalb der Werte, die man für Geburten ohne Medikation voraussagt und berechnet hat. 15 Minuten nach Injektion ist dies am deutlichsten, danach werden Werte wie in der Kontrollgruppe erreicht.

Nicht untersucht wurden die Mechanismen, die zu dem Abfall des $tcPo_2$ sowie den Veränderungen der FHR und uterinen Aktivität führen. Wir vermuten, daß Dolantin® eine Konstriktion der glatten uterinen Gefäßmuskulatur verursacht. Es muß festgehalten werden, daß nach Gabe von 50 mg Dolantin® keine klinisch bedeutsamen FHR- und $tcPo_2$-Veränderungen auftreten. Einigen wenigen Patienten wurden 25 bzw. 75 mg Dolantin® verabreicht; dann wurde bei ihnen das gleiche Monitoring durchgeführt. Bei 25 mg fielen die $tcPo_2$-Spiegel nicht ab; bei 75 mg waren die gleichen Veränderungen wie nach 50 mg zu beobachten, jedoch ausgeprägter.

Schlüsselwörter: Dolantin®, fetale Oxygenierung, FHR-Variabilität, $tcPo_2$, uterine Aktivität.

Résumé

Oxygénation du fœtus humain ($tcPo_2$), instabilité du rythme cardiaque et activité utérine après administration maternelle de mépéridine

La mépéridine est l'analgésique narcotique le plus usuellement utilisé au cours de la phase active du travail. Afin de déterminer l'effet de la mépéridine intra-veineuse sur l'oxygénation fœtale, dix patientes à faible rique ont subi une surveillance continue par voie transcutanée de la pression partielle d'oxygène ($tcPo_2$) pendant la phase active du travail. L'analyse de ces données indique qu'il y a une diminution transitoire des taux de $tcPo_2$ qui commence peu de temps après l'injection intraveineuse de mépéridine et qui atteint le niveau de base post-injection, niveau de base qui est légèrement inférieur aux taux de $tcPo_2$ avant l'injection, environ 15 minutes après l'injection. D'autres analyses de ces données indiquent qu'il existe une relation potentielle entre la diminution des taux de $tcPo_2$ et l'instabilité du rythme cardiaque fœtal (RCF) et l'activité utérine. Dans le but d'examiner cette relation potentielle, on a utilisé un protocole identique chez vingt patiente supplémentaires appariées aux dix patientes d'origine qui avaient eu une surveillance continue de la $tcPo_2$. Ces patientes supplémentaires prises en charge de façon identique (dans le protocole) ont subi une surveillance standard continue avec calcul de l'instabilité quantitative du rythme cardiaque fœtal avec des indices du court terme et du lont terme ainsi que de l'évaluation de l'activité utérine avec mesure de l'aire totale de la courbe de l'activité utérine en utilisant un oscillateur.

La moyenne des taux de $tcPo_2$ en pré-injection était de 18,6 torr, et l'intervalle entre l'injection de mépéridine et le début de la chute initiale était de 3,13 ± 1,75 minutes. L'intervalle entre l'injection de mépéridine et le

point de la baisse maximale était de 9,0 ± 3,55 minutes. La durée de la pente maximale a été de 4,61 ± 3,83 minutes et la valeur la plus basse de $tcPo_2$ a été de 11,7 ± 5,31 torr. Entre l'injection de mépéridine et le retour au niveau de base post-injection, il y a eu un intervalle de 15,29 ± 7,41 minutes avec une diminution en pourcentage de la $tcPo_2$ de 37,4 ± 25,8%. La valeur du niveau de base post-injection était de 15,0 torr. Après mesure de la $tcPo_2$, on a réalisé la mesure du pH capillaire au scalp fœtal que l'on a comparé ensuite aux valeurs des gaz sanguins respiratoires veineux et artériels après la naissance.

Il y a une bonne concordance générale entre le pH capillaire final au scalp fœtal et les dosages des gaz du sang ombilical. Les modifications de la $tcPo_2$ fœtale précèdent une augmentation transitoire minime de l'instabilité du R. C. F. Cette augmentation des paramètres de l'instabilité du R. C. F. est suivie immédiatement par une chute des indices d'instabilité du R.C.F. qui retournent aux valeurs du niveau de base de la même façon que la $tcPo_2$ retourne au niveau de base après la légère baisse post-injection. La mépéridine induit des modifications de la $tcPo_2$ et de l'instabilité du R.C.F. qui sont étroitement liées avec des modifications de la $tcPo_2$ qui précèdent tout juste les altérations de l'instabilité du R. C. F.

Peu de temps après l'injection intra-veineuse de 50 mg de mépéridine les valeurs de l'activité utérine commencent à diminuer en dessous des valeurs positives prévues qui avaient été claculées à partir du travail sans traitement. On en déduit qu'une injection de mépéridine peut entrainer une vaso-constriction transitoire au niveau des muscles lisses vasculaires utérins. Il faut noter qu'à la suite d'une injection intra-veineuse de 50 mg de mépéridine, il n'a pas été observé ni de modification cliniquement significative du rythme cardiaque fœtal, ni des taux de $tcPo_2$. A titre de comparaison, quelques patientes ont reçu soit 25 mg soit 75 mt de mépéridine en intraveineux avec enregistrement de la $tcPo_2$ en pré et en post-injection, surveillance de l'instabilité du R.C.F. et de l'activité utérine.

Les deux patientes ayant reçu 25 mg de mépéridine intraveineuse n'ont pas eu de diminution des taux de la $tcPo_2$; toutefois, la patiente ayant reçu 75 mg a présenté des modifications similaires mais plus accentuées que celles des patientes ayant reçu 50 mg de mépéridine.

Mots-clés: Contraction utérine, instabilité du rythme cardiaque fœtal, mépéridine, oxygénation fœtale, $tcPo_2$.

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